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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,136	10/12/2000	John F. Engelhardt	875.032US1	7933

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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 06/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/689,136	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Daniel Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *13-28 and 37-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8 and 10-12* is/are rejected.

7)☒ Claim(s) *6,9,29-36,83 and 84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Application and Preliminary Amendment filed October 12, 2000, Information Disclosure Statement filed April 18, 2002, and Preliminary Amendment and Response to Restriction Requirement filed April 24, 2002. In response to the restriction requirement mailed October 1, 2001, Applicant has elected invention I (claims 1-12, 29-36, 83 and 84) for examination.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the inventions are so closely related within the context of the disclosure that they cannot properly be considered independent and distinct within the statutory meaning of 35 U.S.C. § 121. Applicant argues that claims directed to a method to identify agents of Formula (I) that alter AAV transduction of mammalian cells are clearly related to claims directed to methods to identify other agents that alter AAV transduction of mammalian cells, and that this is particularly true for claims directed to methods comprising agents of Formula (I) (Groups I, V and IX) and Formula (II) (Groups II, VI and X), as these compounds have structural similarities. This is not found persuasive because, although Formulas I and II are based on a tripeptidic structure with an N-terminal blocking group and a formyl group at the C-terminus, Formula (I) encompasses species that are clearly distinct from species encompassed by Formula (II) and vice versa. Similarly, Applicant's proposal for a revised Restriction Requirement that groups claims directed to methods comprising a peptidic agent versus claims directed to methods comprising a non-peptidic agent is not persuasive because the groupings are overly broad and

clearly encompass patentably distinct material. This is particularly well evidenced by the claims directed to compounds (I) or (II) versus compound (III), which have different biological targets. It is noted, however, that applicant's proposed groupings indicate that he agrees that restriction between methods to identify agents that alter AAV transduction (Groups I-IV) and methods of using an agent to alter AAV trandsuction or expression of a transgene in a cell contacted with an recombinant AAV comprising the transgene (Groups V-XII) is proper. The requirement is still deemed proper and is therefore made FINAL.

The examiner acknowledges that Claim1 link(s) inventions I through IV drawn to methods to identify an agent of Formulas (I)-(IV), respectively, that enhances AAV transduction. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The requirement to elect species is successfully traversed. The elected invention has therefore been examined for the entire genus of compounds encompassed by Formula (I).

Drawings

The drawings are objected to for the reasons provided in the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Specification

The disclosure is objected to because of the following informalities: In the "Brief Description of the Figures", several of the descriptions are inconsistent with the labeling of the figures in that the description refers to panels while the figure labels indicate separate figures. For example, the description of Figure 15 refers to panels A, B and C while the figures referred to are labeled Fig. 15A, Fig. 15B and Fig. 15C.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 8 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claims 7 and 8, the claims are drawn to a method to identify an "endosomal protease inhibitor" that alters adeno-associated virus transduction with claim 8 further limiting the endosomal protease inhibitor to a cysteine protease inhibitor. The metes and bounds of the claims are unclear because "endosomal protease inhibitor" is not a term of art and the specification is silent regarding what properties an endosomal protease inhibitor should have. Obviously the term would exclude compounds that are not capable of inhibiting endosomal proteases. However, the term might also indicate specificity for endosomal proteases and thus exclude compounds that are general inhibitors of cellular proteases or compounds that have more

global effects on cell function. The scope of the invention sought to be patented cannot, therefore be determined from the language of the claims with a reasonable degree of certainty.

With regard to claim 12, the claim is drawn to a method comprising a recombinant adeno-associated virus that comprises a marker gene or a selectable gene. The specification provides definitions for a "detectable marker gene" and a "selectable marker gene". Because the claim uses terminology that is different from the terminology defined in the specification it is not clear what is encompassed by the claimed invention. This is particularly true for "marker gene", which could refer to either a detectable marker gene or selectable marker gene. This rejection can be traversed by amending claim 12 to substitute the terms defined in the specification for the indefinite terms.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by any one of Alexander et al. (1997) U.S. Patent 5,604,090, Russell et al. (1995; IDS 34), Halbert et al. (1997; IDS 23), Qing et al. (1997; IDS 32) or Kessler et al (1995) *Circulation* 92 (Suppl.) I-296.

Claim 1 is drawn to a method to identify an agent that alters AAV transduction of a mammalian cell, comprising: a) contacting the mammalian cell with the agent and virus; and b) determining whether virus transduction is altered. Claim 4 limits the mammalian cell of claim 1

to a human cell, canine cell, murine cell, rat cell or rabbit cell; claim 5 limits the method of claim 1 to a method wherein transduction is enhanced; claim 10 limits the virus of claim 1 to a recombinant adeno-associated virus; claim 11 limits the recombinant virus of claim 10 to a virus that encodes a therapeutic peptide or polypeptide; and claim 12 limits the recombinant virus of claim 10 to a virus that comprises a marker gene or a selectable gene.

Alexander and Russell teach a method to identify an agent that alters AAV transduction of a human fibroblast cell comprising contacting the cell with the agent and recombinant AAV virus comprising a marker gene wherein transduction is enhanced (see especially Alexander column 13, Example 9 and Figure 8; and Russell Figure 1 and the caption thereto). Halbert teaches a method to identify an agent that alters AAV transduction of a mammalian cell (human nasal epithelium and rabbit airway epithelium) comprising contacting the cell with the agent and recombinant AAV virus comprising a marker gene wherein transduction is enhanced (see especially Figures 4 and 5, and the captions thereto). Qing teach a method to identify an agent that alters AAV transduction of a human tumor cell comprising contacting the cell with the agent and recombinant AAV virus comprising a marker gene wherein transduction is enhanced (see especially Figure 5 and the caption thereto). Kessler teaches a method to identify an agent that alters AAV transduction of a rat cardiac myocyte comprising contacting the cell with the agent and recombinant AAV virus comprising a marker gene wherein transduction is enhanced.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Halbert. The claim is drawn to the method of claim 1 wherein the cell is a mammalian lung cell. As described above, Halbert teaches the method of claim 1 wherein the cell is a rabbit airway epithelial cell.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Alexander. The claim is drawn to the method of claim 10 wherein the recombinant virus encodes a therapeutic peptide or polypeptide. Alexander teaches that the method described above comprising recombinant AAV vectors encoding desirable products including "clotting factors, globin gene products, cytokines and growth factors" (see especially column 6, "COMMERCIAL UTILITY").

The method, cell and recombinant AAV vector of Alexander, Russell, Halbert, Qing and Kessler are the same as those taught in the instant application, therefore the limitations of the claims are met by the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander in view of Snyder et al. (1998) WO 98/24479. The limitations of claims 1, 4, 5, 10 and 11 are recited above. Claim 3 is drawn to the method of claim 1 wherein the cell is a mammalian liver cell. As argued above, Alexander teaches all of the limitations of the claims except a mammalian liver cell. Snyder (1998a) teaches methods comprising AAV transduction of "cells of the hepatic system of a mammal" (see especially page 22, "Target Cells"). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of identifying an agent that alters adeno-associated virus transduction of mammalian cells taught by Alexander to include transduction of cells of the hepatic system taught by Snyder. Motivation to combine these teachings comes from Snyder who teaches, "there is a tremendous need for safe and effective vectors for transducing normal liver cells" (page 10, line 11) and from Alexander who teaches, "Increased transduction, particularly of non-dividing cells, can facilitate gene transfer and is useful in many applications, including...therapeutic applications" (column 2, lines 15-17). One would have a reasonable expectation of success in combining these teachings because maintenance of liver cells in culture is well known in the art and the method of Alexander can be readily applied to any cultured cell.

Allowable Subject Matter

Claims 6, 9, 29-36, 83 and 84 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 7 and 8 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
June 20, 2002

JAMES KETTER
PRIMARY EXAMINER